# To the G20:

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# To the G20 – Next steps for incentivizing antibacterial R&D

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The antibiotic pipeline is insufficient. As one measure, only about five truly novel antibiotic classes are in clinical development for critical or high unmet public health needs defined by the World Health Organization.[1,2] Given attrition rates[3], only two of these are likely to receive regulatory approval during the next seven years. The earlier, pre-clinical phase pipeline is hard to assess, but may include more than a dozen novel antibiotics. However, their chances of success are even more remote and likely more than a decade away.[3] Meanwhile, resistance rates to the world's current stock of antibiotics are rising, threatening not only our ability to treat infections but also jeopardizing modern healthcare's ability to safely treat cancer and perform many surgeries.[4,5] Deliberate and coordinated action is needed now to ensure continuous availability of effective antibiotics.

Box 1: Next steps for G20 members to incentivize antibacterial R&D

- Immediately fill the gap of USD 250 million per year in push funding. Existing mechanisms require additional financing and are well suited for an immediate in-flow of extra financing.
- Implement Market Entry Reward (MER) pilots in order to learn about the operationalization of such models.
- Request that regional and global banking institutions (such as the European Investment Bank and the World Bank) examine potential novel financial instruments to support further antibacterial R&D funding.
- Establish a mechanism for multi-national coordination and collaboration.
- Develop health technology assessment processes and rules of reimbursement to consider resistance situation and capture antibiotic societal value.

In 2016, the G20 committed to "*unlock research and development into new and existing antimicrobials from a G20 value-added perspective*".[6] DRIVE-AB, a three-year research project financed by the European Union's Innovative Medicines Initiative, is close to concluding its work on incentives and policies to stimulate innovation, sustainable use, and equitable availability of novel antibiotics to meet unmet public health needs. This commentary summarizes some of DRIVE-AB's findings pertinent to the G20 commitments, including a Market Entry Reward (MER). DRIVE-AB's complete findings will be published and presented at our conference in Brussels on September 5-6, 2017. These include detailed findings and recommendations regarding new economic models, the societal value of antibiotics, forecasting the development of resistance, and responsible use measures.

Incentives to stimulate antibacterial innovation can be grouped into two types: "push" incentives that pay for the research and development (R&D) and "pull" that reward an outcome such as regulatory approval. Significant investments are already occurring to push innovation, including grant financing such as the Biomedical Advanced Research and Development Authority (BARDA), Innovative Medicines Initiative (IMI), Joint Programming Initiative on Antimicrobial Resistance (JPIAMR), the Horizon 2020 research programme, and most recently the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) and the Global Antibiotic R&D Partnership (GARDP) that acts as a virtual developer. These efforts are laudable, necessary and must continue. They ensure that the pipeline is directed to public health needs. Yet the success of these

initiatives in bringing novel antibiotics to market depends on continued private investment. Our stakeholder analyses identify that the willingness of companies and other private investors to invest in antibacterial R&D is primarily driven by anticipated market rewards, i.e. the pull incentives.

The traditional pull incentive is revenues from unit-based sales. Yet for new antibiotics, revenues alone may not be sufficient to incentivize companies to invest in the development of new antibiotics. In clinical practice, it is appropriate to reserve novel antibiotics for use against bacteria that are resistant to existing antibiotics. If infection prevention efforts are successful, such infections may be relatively rare, so sales volumes will be low. Therefore, new pull incentives are needed that effectively reward innovation and reduce revenues derived from sales volume – a "delinked" model. Without an effective pull incentive, private sector investment will continue to decline, and the few remaining companies will leave antibacterial R&D, further diminishing innovation.

A fully or partially delinked MER (i.e., a financial payment to the developer or IP holder for a novel antibiotic that meets predefined target product profile addressing the most pressing public health threats) can be an effective pull mechanism. The decision on behalf of an innovator to apply for a MER will be voluntary. The size of the reward should be commensurate with the level of pre-defined need using public health criteria such as the World Health Organization's Priority Pathogen List. Additionally, those antibiotics that meet more challenging criteria such as a new class should receive higher rewards.[7] Based on our current models (final versions to be presented in September 2017), we estimate a MER of between USD 750 to 2,000 million, paid out to developers in installments over five years. Grants from public funds and foundations for preclinical and clinical trials must be accounted for in calculating the MER so that the public does not pay twice for innovation. Developers that receive a MER will also be bound by transparent and implementable sustainable use and equitable access obligations.

While significant public sector investment in antibacterial R&D is already occurring, estimated at USD 520 million annually,[7] our models suggest that the public and philanthropic sectors must invest an additional USD 250 million in push funding annually into targeted priority antibacterial R&D areas[1] to maintain a healthy pipeline. This excludes investments in diagnostics, vaccines, or products for animal health, which are also needed. Banking institutions such as the European Investment Bank and the World Bank could raise capital by financing medicines in other therapeutic areas and utilizing a portion of the returns to re-invest in antibiotics.

Private investment must also increase. The implementation of a MER will help attract and retain private capital. Additionally, health technology assessment procedures need to be expanded to account for drug resistance prevalence and to capture the societal benefit of a specific antibiotic, allowing for value-based pricing based on societal benefits of the particular antibiotic (e.g., resistance and cross-resistance rates). With these incentives, our models suggest that private sector investment will at least double the public sector push contribution.

Implementation of a MER is complex and unprecedented. DRIVE-AB and others[8-10] have extensively explored multiple implementation options, ranging from country level arrangements to the transfer of intellectual property to a global organization. All options have their pros and cons and cost/benefit implications. These will be fully articulated in our final report.

Setting up infrastructure to implement MERs will take financial investment and time. We see that different models can be introduced as infrastructure and expertise is built up. In the near term, different national and multi-national solutions need to be designed to work synergistically with others. Piloting MERs can help to understand these synergies and the operationalization. Yet implementing a forum for global coordination is urgent, as innovators need clear messages about

global priorities. Next steps for incentivizing antibacterial R&D that can be taken by the G20 countries immediately are noted in Box 1. DRIVE-AB's detailed recommendations will be available in September.

1. World Health Organization. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and the development of new antibiotics. Geneva: World Helath Organization, 2017.
2. Pew Charitable Trust. Antibiotics Currently in Clinical Development. 2016. http://www.pewtrusts.org/en/multimedia/data-visualizations/2014/antibiotics-currently-in-clinical-development (accessed 2016/08/09 2016).
3. Payne DJ, Gwynn MN, Holmes DJ, Pompliano DL. Drugs for bad bugs: confronting the challenges of antibacterial discovery. *Nature reviews Drug discovery* 2007; **6**(1): 29-40.
4. Teillant A, Gandra S, Barter D, Morgan DJ, Laxminarayan R. Potential burden of antibiotic resistance on surgery and cancer chemotherapy antibiotic prophylaxis in the USA: a literature review and modelling study. *The Lancet infectious diseases* 2015.
5. Skov R, Monnet D. Plasmid-mediated colistin resistance (mcr-1 gene): three months later, the story unfolds. *Eurosurveillance* 2016; **21**(9).
6. G20. G20 Leaders' Communiqué: Hangzhou Summit. Hangzhou, China: G20, 2016.
7. OECD W, FAO, OIE,. Tackling Antimicrobial Resistance, Ensuring Sustainable R&D. *(draft)* 2017.
8. AMR Review. Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. London: The Review on Antimicrobial Resistance, 2016.
9. Rex JH, Outterson K. Antibiotic reimbursement in a model delinked from sales: a benchmark-based worldwide approach. *The Lancet infectious diseases* 2016; **16**(4): 500-5.
10. The Boston Consulting Group. Breaking through the Wall: A Call for Concerted Action on Antibiotics Research and Development, 2017.